REMARKS

Entry of the foregoing and reconsideration of the subject application are respectfully requested in light of the amendments above and the comments which follow.

Entry of this Amendment is proper under 37 C.F.R. § 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not raise any new issue requiring further search and/or consideration because the amendments amplify issues previously discussed throughout prosecution; does not present any additional claims; relates to matters of form rather than substance because the added language was already present in the claims; and places the application in better form for an appeal should an appeal be necessary. The Amendment is necessary and was not earlier presented, because it is made in response to arguments raised in the final rejection. Entry of the Amendment, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are thus respectfully requested.

The amendments are made without disclaimer or prejudice to Applicants' rights to pursue any canceled subject matter in this or a timely-filed continuing application.

1. Status of the Claims

Claims 9-19 and 23 are pending. Upon entry of the present amendment, claims 1-12 and 16-19 are cancelled.

Claims 13-15 and 23 are under examination.

2. Support for Claim Amendments

Claims 13 and 23 have been amended to recite that the nucleic acid sequence encodes a polypeptide. The amendment is supported in the specification, for instance, on p. 27, lines 23-24; and p. 28, lines 4-10.

Accordingly, the amendment to the claims does not introduce new matter.

3. Rejection under 35 U.S.C. § 112, 2nd paragraph

The Office has rejected claims 13-15, 19 and 23 under 35 U.S.C. §112, 2nd paragraph as allegedly being vague and indefinite. Claim 19 has been cancelled, mooting its rejection. With regard to claim 13, the Office alleges that the phrase "wherein said nucleic acid is at least 95% identical to SEQ ID No.: 2" is confusing because SEQ ID NO: 2 is an amino acid sequence.

Applicants have amended claim 13 to make clear that the nucleic acid encodes a polypeptide that is at least 95% identical to SEQ ID No. 2.

Reconsideration and withdrawal of the rejection is requested.

4. Rejection under 35 U.S.C. §103(a)

The Office has maintained the rejection of claims 13-15 and 23 under 35 U.S.C. §103(a) as being obvious over Short et al (U.S. Pat. No. 6,720,014; "**Short**") in view of Berka et al. (U.S. Pat. No. 6,221,644; "**Berka**") and van der Laan et al. (1991, Appl Environ Microbiol. 57:901-909; "**van der Laan**").

The Office has rejected Applicants' arguments for the following reasons. With regard to Short, the Office asserts that "the amount of additional teaching...that is not within the scope of the claims is irrelevant to the inquiry of whether it would be obvious to modify one particular disclosed method." The Office further alleges that it is irrelevant if Short teaches other methods of making variant phytase genes.

These assertions are incorrect as a matter of law. As pointed out in MPEP 2141.02, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention," citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (emphasis added). Furthermore, the *KSR* court held that a combination that was "obvious to try" may indicate obviousness if there are a finite number of identified, predictable solutions and the person of ordinary skill in the art has good reason to pursue the known options within his/her technical grasp, and this pursuit leads to the anticipated success. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Thus the law requires that the entirety of the teachings in Short be considered, including the number of possible solutions. Therefore, it is entirely relevant to the evaluation of obviousness that Short teaches a wide variety of methods to produce variants: error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, in vivo mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis, site-specific mutagenesis, ligation reassemble, GSSM, synthetic ligation reassembly (SLR), in vivo shuffling and combinations thereof. Short teaches a myriad of possible solutions for producing variants. Short discusses the SLR method at length. See, e.g., col. 19, line 58- col. 20, line 41; col. 21, line 1 et seq.; and col. 22, line 25 et seq. In notable contrast, however, Short does not, however, point out error-prone amplification with any particularity. Thus, the ordinarily skilled artisan, presented with the myriad possible solutions to produce variants of phytase by Short, would have been guided by Short's detailed discussion of the synthetic ligation reassembly process to produce phytase variants using that process.

The Office further alleges that the fact that Berka teaches that a signal sequence is not a necessary control sequence for expression does not detract from the Short's teaching that a signal sequence can be used. The Office alleges that the ordinarily skilled artisan would have had a clear reason to utilize a signal sequence because the signal sequence is necessary to secrete the phytase from a recombinant host and the secretion simplifies isolation as secreted proteins are a small portion of the total protein produced by a host cell. By this reasoning, however, the ordinarily skilled artisan would not have deliberately subjected the signal sequence to any mutational process, because such mutation is likely to eliminate the signal sequence activity. Eliminating the signal sequence activity would contravene the advantage of using a signal sequence. Therefore, contrary to the Office's allegation, while the ordinarily skilled artisan may have utilized a signal sequence in connection with an already-mutated coding sequence, the same artisan would not subject a nucleic acid encoding a signal sequence and a phytase to error-prone amplification, because this would undo the advantages afforded by the presence of a signal sequence.

The Office further alleges that "the issue in the instant rejection is whether one of skill in the art would have found it obvious to select the signal sequence of van der Laan et al. for use with the method of making variant phytases..." Preliminarily, it is noted that the Office appears to be reducing the invention to a global thrust or gist. Such a distillation is improper. Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter "as a whole." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Moreover, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). Furthermore, guidance or lack thereof in directing a person of ordinary skill in the art to a particular solution must also be considered (*Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007)). The Office fails to consider the *lack of guidance* in the art that would have led the ordinarily skilled artisan to modify the sequence of a naturally occurring mature phytase to replace its endogenous signal sequence with another signal sequence, and then subject the resulting hybrid nucleic acid to error-prone amplification process, transforming a host cell with a product of the error-prone amplification and culturing the transformed cell.

None of Short, Berka or van der Laan provides *guidance with particularity* for modifying a naturally occurring phytase coding sequence to comprise the signal sequence of the alkalophilic strain *B. alcalophilus* PB92 disclosed by van der Laan. As discussed in the previous response, Berka teaches that a signal sequence is not necessary for expression of a coding sequence and is therefore optional. Additionally, Berka discloses a large variety of signal sequences known in the art. Exemplary signal sequences taught by Berka can be obtained from a glucoamylase or an amylase gene from an *Aspergillus species*, a lipase or proteinase gene from a *Rhizomucor* species, the gene for the alpha-factor from *Saccharomyces cerevisiae*, an amylase or a protease gene from a *Bacillus* species, or the calf preprochymosin gene. Regarding bacterial expression, Berka describes the following as

effective signal peptides: the signal peptide coding region obtained from the maltogenic amylase gene from Bacillus NCIB 11837, the *Bacillus stearothermophilus* alpha-amylase gene, the *Bacillus licheniformis* subtilisin gene, the *Bacillus licheniformis* beta-lactamase gene, the *Bacillus stearothermophilus* neutral proteases genes (nprT, nprS, nprM), and the *Bacillus subtilis* PrsA gene. Berka teaches generically that a coding sequence may contain a signal peptide coding region which is foreign to that portion of the coding sequence which encodes the secreted polypeptide. Berka explicitly states that "...the foreign signal peptide coding region may simply replace the natural signal peptide coding region in order to obtain enhanced secretion of the phytase relative to the natural signal peptide coding region normally associated with the coding sequence." See col. 12, lines 18-23. Notably, however, with regard to the signal sequence taught by van der Laan, and as noted by the Office, van der Laan expressly states that the signal sequence is comparable to other Bacillus signal sequences. Hence, Van der Laan does not teach or suggest that the signal sequence of *B. alcalophilus* PB92 is any different from any other Bacillus signal sequence, or provide any advantage or improvement such as the enhanced secretion taught by Berka, that would have guided the ordinarily skilled artisan to chose the signal sequence of *B. alcalophilus* PB92 out of the very many signal sequences known in the art. Thus, neither Berka nor van der Laan teach or suggest that the signal sequence of the alkalophilic strain *B. alcalophilus* PB92 would be particularly useful for expression and secretion of a phytase. There is simply no basis for an ordinarily skilled artisan to have selected the signal sequence of *B. alcalophilus* PB92 over any of the plethora of signal sequences known in the art to modify the *E. coli* phytase disclosed by Short.

In summary, there are a myriad of possible solutions, both in terms of method steps and starting nucleic acid material, for preparing variants of a phytase sequence in view of Short and Berka. There is, however, a virtually complete lack of guidance in the art to combine the elements in the way the claimed new invention does. Specifically, there is no guidance leading the ordinarily skilled artisan to produce a recombinant phytase having modified activity by subjecting to error-prone amplification a nucleic acid encoding a naturally occurring *E. coli* phytase that has been modified to replace its endogenous signal

sequence with the signal sequence of *B. alcalophilus* PB92; transforming a host cell with an expression construct comprising the product of error-prone amplification and culturing the transformed cell to express the product.

The combination of Short, Berka and van der Laan cannot and does not render the claims obvious. The Office's obvious-to-try rationale cannot be used to support a conclusion that the claims would have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejection is requested.

CONCLUSION

The claims are believed in condition for allowance, which is requested in light of the amendment and remarks above. Should the Office have any questions or comments regarding the amendments or response, please contact Applicants' undersigned representative.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayments to Deposit Account 50-0573. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3). If no further response is filed before March 23, 2011, then this paragraph is intended to be a **CONSTRUCTIVE NOTICE OF APPEAL** in accordance with 37 C.F.R. § 41.31(a)(1).

Applicants' representative is signing in her capacity under 37 C.F.R. §1.34 on behalf of Applicants.

Respectfully Submitted,

Date: January 14, 2011 By: _____

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